CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074878

Trade Name : PENTOXIFYLLINE EXTENDED RELEASE TABLETS 400MG

Generic Name: Pentoxifylline Extended Release Tablets 400mg

Sponsor : Purepac Pharmaceutical Co.

Approval Date: July 9, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074878

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074878

APPROVAL LETTER

ANDA 74-878

JUL 9 1997

Purepac Pharmaceutical Co.
Attention: Joan Janulis, R.A.C.
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated March 29, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Pentoxifylline Extended-release Tablets, 400 mg.

Reference is also made to your amendments dated June 28, August 2, and November 27, 1996 and June 12, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Pentoxifylline Extended-release Tablets, 400 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Trental® Tablets 400 mg of Hoechst Marion Roussel Inc.).

The "interim" dissolution test and tolerances are:

> USP 23 apparatus 2 at 50 rpm; 900 mL water/37°C; NMT at 1 hour, at 3 hours, at 8 hours, NLT at 18 hours of the label amount is dissolved.

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70 (c)(1) when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under 21 CFR 314.70 (b)(2)(ii).

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the changes may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

7/9/97

Douglas L./ Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074878

FINAL PRINTED LABELING

SAMPLE

40-8803

PENTOXIFYLLINE EXTENDED-RELEASE TABLETS

[redacted]

Revised — October 1996

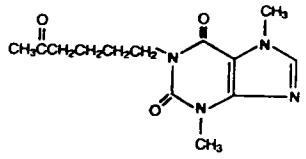
JUL - 9 1997

9 1997

DESCRIPTION:

Pentoxifylline Extended-Release Tablets for oral administration contain 400 mg of the above drug and the following inactive ingredients: D&C yellow #10 aluminum lake, FD&C yellow #6 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maltodextrin, polyethylene glycol, povidone, talc, titanium dioxide, and triacetin.

Pentoxifylline is a tri-substituted xanthine derivative designated chemically as 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione that, unlike theophylline, is a hemorrheologic agent, i.e. an agent that affects blood viscosity. Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene. The chemical structure is:



$C_{13}H_{18}N_4O_3$ M.W. 278.31

CLINICAL PHARMACOLOGY:

Mode of Action: Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leukocyte properties of hemorrheologic importance have been modified in animal and *in vitro* human studies. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease.

Pharmacokinetics and Metabolism: After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing. Peak plasma levels of the parent compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxyhexyl]-3,7-dimethylxanthine) and Metabolite V (1-[3-carboxypropyl]-3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than pentoxifylline.

Following oral administration of aqueous solutions containing 100 to 400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose-related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4 to 0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (Cytochrome P_{450}) following multiple oral doses.

Excretion is almost totally urinary; the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces.

Food intake shortly before dosing delays absorption of an immediate-release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of pentoxifylline have not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years).

After administration of the 400 mg controlled-release pentoxifylline tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2 to 4 hours and remain constant over an extended period of time. The controlled release of pentoxifylline from the tablet eliminates peaks and troughs in plasma levels for improved gastrointestinal tolerance.

INDICATIONS AND USAGE:

Pentoxifylline extended-release tablets are indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Pentoxifylline can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:

Pentoxifylline should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:

General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Pentoxifylline has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that pentoxifylline causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including, hematocrit and/or hemoglobin.

Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with pentoxifylline with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Concomitant administration of pentoxifylline and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals. Such patients should be closely monitored for signs of toxicity and have their theophylline dosage adjusted as necessary. Pentoxifylline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifylline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to 450 mg/kg (approximately 19 times the maximum recommended human daily dose (MRHD) in both species when based on body weight; 1.5 times the MRHD in the mouse and 3.3 times the MRHD in the rat when based on body-surface area). In mice, the drug was administered for 18 months, whereas in rats, the drug was administered for 18 months followed by an additional 6 months without drug exposure. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females of the 450 mg/kg group. The relevance of this finding to human use is uncertain. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) and in cultured mammalian cells (unscheduled DNA synthesis test) when tested in the presence and absence of metabolic activation. It was also negative in the *in vivo* mouse micronucleus test.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Teratogenicity studies have been performed

in rats and rabbits, using oral doses up to 576 and 264 mg/kg, respectively. On a weight basis, these doses are 24 and 11 times the maximum recommended human dose (MRHD); on a body-surface-area basis, they are 4.2 and 3.5 times the MRHD. No evidence of fetal malformation was observed. Increased resorption was seen in rats of the 576 mg/kg group. There are no adequate and well controlled studies in pregnant women. Pentoxifylline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

Clinical trials were conducted using either extended-release pentoxifylline tablets for up to 60 weeks or immediate-release pentoxifylline capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200 to 400 mg tid.

The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received extended-release pentoxifylline tablets, immediate-release pentoxifylline capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the extended-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Extended-Release Tablets — Commercially Available		Immediate-Release Capsules — Used only for Controlled Clinical Trials	
	Pentoxifylline	**Placebo**	**Pentoxifylline**	**Placebo**
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	-	1.1	2.2
Arrhythmia/Palpitation	-	-	1.7	0.7
Flushing	-	-	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	-	-	4.0	1.4
Belching/Flatus/ Bloating	0.6	-	9.0	3.6
Diarrhea	-	-	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	-	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	-	-	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	-	-	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	-	-	2.3	2.2
Tremor	0.3	0.8	-	-
Blurred Vision	-	-	2.3	1.4

Pentoxifylline has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:

Cardiovascular - dyspnea, edema, hypotension.

Digestive - anorexia, cholecystitis, constipation, dry mouth/thirst.

Nervous - anxiety, confusion, depression, seizures.

Respiratory - epistaxis, flu-like symptoms, laryngitis, nasal congestion.

Skin and Appendages - brittle fingernails, pruritus, rash, urticaria, angioedema.

Special Senses - blurred vision, conjunctivitis, earache, scotoma.

Miscellaneous - bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: "Cardiovascular - angina, arrhythmia, tachycardia, anaphylactoid reactions." Digestive - hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic - decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

OVERDOSAGE:

Overdosage with pentoxifylline has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.

In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to absorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:

The usual dosage of pentoxifylline in extended-release tablet form is one tablet (400 mg) three times a day with meals.

While the effect of pentoxifylline may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.

Digestive and central nervous system side effects are dose related. If patients develop these effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of pentoxifylline should be discontinued.

HOW SUPPLIED:

Pentoxifylline Extended-Release Tablets are available as follows:

400 mg — Each unscored yellow, oblong, film coated tablet imprinted R611 contains 400 mg of pentoxifylline. Tablets are supplied in bottles of 100 (NDC 0228-2611-11), 500 (NDC 0228-2611-50), and 1000 (NDC 0228-2611-96).

Dispense in well-closed, light-resistant containers with safety closures.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

40-8803

Revised — October 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074878

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-878

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
Attention: Joan Janulis, R.A.C.
200 Elmora Avenue
Elizabeth, NJ 07207

4. LEGAL BASIS for ANDA SUBMISSION
Referenced Listed Drug: Trental® Extended-release Tablets 400 mg;
Hoechst-Roussel Pharmaceuticals, Inc. (N18631, approved 8.30.84)
Patent Certification: page 7; Expire 2.2.97 & 4.3.97
Exclusivity: page 9; none

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Pentoxifylline Extended-release Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: None

9. AMENDMENTS AND OTHER DATES:

Firm:

03.29.96 - Original
11.27.96 - Amendment
06.12.97 - Amendment **Subject of this review**

FDA:

04.25.96 - Acceptable for filing
10.21.96 - NA letter #1
06.12.97 - NA letter #2

10. PHARMACOLOGICAL CATEGORY
Vasodilator

11. Rx or OTC
Rx

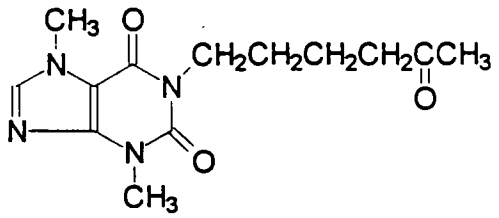
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Extended-release Tablets

14. POTENCY
400 mg

15. CHEMICAL NAME AND STRUCTURE

Pentoxifylline



1-(5-oxohexyl)-3-7- dimethylxanthine

$C_{13}H_{18}N_4O_3$ 278.31

16. RECORDS AND REPORTS none

17. COMMENTS

a. CMC satisfactory.
b. Professional Labeling - Acceptable, A. Payne, 6.6.97
c. Non-compendial, MV acceptable, Philadelphia District, 7.29.96, Anna Lazar, chemist.
d. Bio-review Satisfactory, letter out 10.31.96, reviewer Lin-whei Chuang,
e. EER satisfactory 10.30.96.

18. CONCLUSIONS AND RECOMMENDATIONS No chemistry deficiencies remaining and the application is approvable.

19. REVIEWER: U. V. Venkataram
DATE COMPLETED: 6.23.97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074878

BIOEQUIVALENCE REVIEW(S)

ANDA 74-878

Purepac Pharmaceuticals Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth NJ 07207

OCT 31 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Pentoxifylline Extended-release Tablets 400 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   "NMT at 1 hour , at 3 hours, at 8 hours, NLT , at 18 hours, of the label amount of pentoxifylline are dissolved"

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 2 8 1996

Pentoxifylline
400 mg Extended Release Tablet
ANDA 74-878
Reviewer: L. Chuang

Purepac Pharmaceutical Co.
Elizabeth, NJ
Submission Date:
March 29, 1996,
June 28, 1996,
August 2, 1996

Review of Three Bioequivalence Studies and Dissolution Data

Introduction:

Pentoxifylline is a hemorrheologic agent that improves the flow properties of blood by decreasing its viscosity and improving erythrocyte flexibility. These actions increase blood flow and enhance tissue oxygenation in patients with chronic peripheral arterial disease. It is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs.

Pentoxifylline is a trisubstituted xanthine derivative structurally related to other xanthines (e.g., caffeine, theophylline). It is designated chemically as 1-(5-oxohexyl)-3,7-dimethylxanthine. The pKa is 0.28 and the water solubility at 25° is about 77 mg/mL.

Administration of single doses (400 mg) of pentoxifylline ER tablets results in T_{max} values of 2-4 hr and mean C_{max} values of 55-300 ng/mL. In one study, the apparent mean half-life of parent drug was about 3.4 hr which demonstrates the absorption-limited elimination rate of the extended release dosage form. In contrast, mean half-lives after 200-400 mg single doses of immediate-release dosage forms have been reported as follows : capsule, 0.89 hr; solution, 0.84 hr; intravenous, 1-1.6 hr. After multiple dosing of pentoxifylline ER tablets (400 mg every 8 hours for 6-7 days), mean steady-state values of pentoxifylline C_{max} were 189-248 ng/mL and T_{max} was 0.9-2 hours.

Pentoxifylline may undergo extensive first-pass metabolism by both oxidation and reduction pathways to form several metabolites. A reduction pathway results in 1-(5-hydroxyhexyl)-3,7-dimethylxanthine (M1) which may attain plasma levels 2-5 times higher than the parent drug. An oxidation pathway results in 1-(3-carboxypropyl)-3,7-dimethylxanthine (M5) which may attain plasma levels 5-8 times greater than the parent drug. More than 90% of a pentoxifylline dose is eliminated renally as metabolites.

M1 has pharmacological properties that are equal in potency to the parent drug. Based on human erythrocyte filterability studies, M1 and M5 were more active hemorrheologic agents than the parent compound.

The effects of food on pentoxifylline kinetics were studied with an immediate-release capsule. For both parent drug and M1: 1) changes in AUC_{0-10} and AUC_{0-inf} were not significant; 2) mean

C_{max} was decreased significantly after food; 3) mean T_{max} was increased significantly.

Pentoxifylline is available as Trental® (Hoechst-Roussel) 400 mg extended-release (ER) tablet. The usual dosage is one tablet three times a day with meals.

The original ANDA was submitted by the firm on 03/29/96. Additional information (data diskett and stability data) were submitted on 06/28/96 and 08/02/96 per request by the Office.

Bioequivalence Study -- Single Dose -- Fasted -- 2-Way Crossover

The objective of this study was to compare the single-dose bioavailability of Purepac and Hoechst-Roussel (Trental^R) 400 mg pentoxifylline extended release tablets under fasted condition.

The clinical study was conducted at
during 09/23-10/02/95 with as co-principal
investigators. The analytical study was conducted at
during 10/11-12/18/95 by analysts

The design of the study was a single-dose, 2-way crossover in fasting non-smoking male volunteers. The protocol and the informed consent form were approved by Institutional Review Board on September 13, 1995.

Thirty-eight (36 plus 2 alternates) non-smoking male volunteers, 18-40 years old, were enrolled. They consisted of 22 Caucasians, 15 African-American and 1 Asian-American. Each volunteer completed the screening process within 28 days prior to period 1 dosing. The inclusion criteria were:

1. male, 18-45 years old, non-smoking
2. clinically normal laboratory profile, which included hematology, serum chemistry, urinalysis, HIV test, hepatitis B surface antigen test, urine drug screen and urine alcohol test at period 1 check-in, and EKG.

The exclusion criteria were:

1. history or presence of any significance disease, especially hypersensitivity to pentoxifylline or any other xanthines, arrhythmias, hypotension, bleeding disorders, peptic ulcers and alcoholism or drug abuse within the last year.
2. blood pressure lower than 110/70 mmHg at screening or lower than 100/60 mmHg before dosing.
3. abnormal diet during the 4 weeks preceding the study
4. donation of excessive amount of blood during the past year.
5. participation in another clinical trial within 28 days of study start.

Volunteers were instructed of the following restrictions:

1. not to take any prescription medication for 14 days preceding the study and during the

washout period.

2. not to take any OTC medications for 7 days preceding the study and during the washout period.
3. not to consume any xanthine or alcohol-containing products within 48 hours prior to each dosing and throughout the period of confinement.

Subjects were confined to the clinical facility from 10 hours before to 36 hours after dosing. After an overnight fast of 10 hr, on the morning of 09/24/95, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Pentoxifylline extended-release tablet, 1 x 400 mg, Purepac Pharmaceutical Co., lot #PI-890, potency 100.4%, manufacturing date 09/07/95, lot size of

Treatment B - Reference Drug: Trental[R] tablet, 1 x 400 mg, Hoechst-Roussel, lot #0781865, expires 05/97, potency 100.5%.

After a 7-day washout, on 10/01/95, each subject was crossed over to the alternative treatment. Subjects remained fasted and engaged in normal activity for 4 hours after dosing. Safety monitoring included measurements of body temperature prior to dosing, and vital signs (pulse rate, blood pressure and respiration rate) prior to dosing and at 2 hours after dosing.

Blood samples (10 mL each) were collected in Vacutainers containing EDTA before dosing and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 30, and 36 hours. Plasma samples were prepared, frozen, and stored at -12°C pending shipment to the analytical site. The storage temperature at the analytical site was -22°C. Each subject received a physical examination following the 36-hour blood draw in period 2.

Analytical Method -- **Not for Release through FOI**:

Results:

Of the 38 subjects enrolled, subject #2 withdrew from the study 1.5 hours after period 2 (treatment B) dosing due to diarrhea, vomiting and pain at venipuncture site. These adverse effects were probably drug-related and definitely procedure-related.

Excluding the adverse events reported by subject #2, 5 adverse events were reported by 3 subjects, 2 during treatment A and 3 during treatment B. The complaints involved headache, nausea, feeling faint after blood draw, and pain at venipuncture.

Some protocol deviations were judged unlikely to affect the bioavailability comparison, i.e., delay or early blood sampling which were time adjusted in the concentration-time profile, meal schedule deviations and the omission of some items of the post-study laboratory test for some subjects.

During the physical examination following the 36-hour blood draw in period 2, some laboratory tests were inadvertently omitted. The rest of the results were either within normal limits or judged by the medical officer to be not clinically significant.

The plasma samples from 36 subjects (first 18 subjects from each sequence who completed the study, i.e. subjects #1, 3-37)) were assayed for pentoxifylline, M5 and M1. Four (4) plasma samples were lost during processing, i.e., 24-hour sample of #29, 1-hour sample of #5, 10--hour sample of #11, and pre-dose of #24, all from treatment B.

Among the 1509 study samples analyzed, reassay was conducted because of anomaly of the original values in 14 samples for M5, 15 for M1, and 50 for pentoxifylline. Each repeated sample was reassayed either once or twice, depends on the amount of plasma sample available. The results of the repeated assay were mostly within 20% of the original values, and either the median or the original value was reported. Only 1 sample for M5 and 3 samples for pentoxifylline were reported as "not reportable" and their final values were interpolated since the repeated results were more than 30% from the original values.

The results of all 3 analytes for subject #37, 2.5-hour, treatment B, were reported as "missing" because the plasma tubes were received with non-GLP labels, i.e., not initialed or dated.

The mean plasma concentrations of M5, M1 and pentoxifylline at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Figures 1-3 and Tables 4-6. The elimination constant used to calculate AUC_{0-inf} was obtained by linear least-square regression analysis using the last 3 non-zero points. No value of AUC_{0-inf} or $T_{1/2}$ was reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile. Some concentration values were considered to be pharmacokinetic anomalies, i.e. 5 samples for pentoxifylline, and 1 sample each for M1 and M5. These values were set to be missing for pharmacokinetic and statistical analyses. None of these missing values were near C_{max}.

Table 4: Mean (C.V.%) Plasma Pentoxifylline Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 36[a] - 400 mg ER Tablet - Fasting Study)

Time (hour)	Purepac (Treatment A)	Hoechst-Roussel (Treatment B)
0	0	0
0.33	39.25 (63)	32.20 (79)
0.67	62.07 (46)	55.01 (60)
1.00	55.51 (45)	48.83[b] (52)
1.50	55.94 (41)	46.61 (44)
2.00	51.53 (48)	40.68 (44)
2.50	48.58[b] (52)	40.24[b] (50)
3.00	45.12 (65)	39.60 (51)
3.50	40.24 (53)	39.18 (55)
4.00	33.47 (61)	33.63 (51)

4.50	42.35 (61)	42.10 (49)
5.00	33.97[b] (55)	34.85 (60)
6.00	23.93 (59)	29.40[c] (61)
8.00	21.12[b] (61)	25.68 (69)
10.00	19.66[b] (61)	28.24[b] (75)
12.00	23.37[b] (85)	20.72 (79)
16.00	13.96 (75)	12.71 (90)
20.00	3.79 (164)	3.38 (162)
24.00	0.53 (424)	0.44[b] (332)
30.00	0	0
36.00	0	0
AUC_{0-t} (ng*hr/mL)	472.5 (50)	475.4 (55)
AUC_{0-inf} (ng*hr/mL)	690.9[a] (35)	610.5[d] (49)
C_{max} (ng/mL)	76.76 (38)	68.96 (45)
$LNAUC_{0-t}$	415.6[f] (58)	413.1[f] (60)
$LNAUC_{0-inf}$	648.0[a,f] (40)	541.5[d,f] (56)
LNC_{max}	70.88[f] (44)	61.87[f] (53)
T_{max} (hour)	1.39 (85)	2.06 (113)
$T_{1/2}$ (hour)	5.43[a] (55)	4.22[d] (49)

a = unless otherwise indicated: b = (n=35), c = (n=34), d = (n=19), e = (n=13)
f = geometric mean

Table 5: Mean (C.V.%) Plasma M1 Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 36[a] - 400 mg ER Tablet - Fasting Study)

Time (hour)	Purepac (Treatment A)	Hoechst-Roussel (Treatment B)
0	0	0
0.33	46.17 (71)	39.91 (87)
0.67	143.28 (35)	129.50 (52)
1.00	200.96 (33)	176.91[b] (44)
1.50	246.05 (34)	221.16 (37)
2.00	264.20 (36)	231.37 (37)

2.50	263.81	(38)	226.54[b]	(36)
3.00	257.77	(42)	227.88	(39)
3.50	244.33	(45)	218.31	(41)
4.00	224.53	(48)	211.59	(44)
4.50	196.57	(50)	195.45	(42)
5.00	172.45	(50)	173.24	(44)
6.00	134.12	(53)	145.62	(51)
8.00	88.62	(46)	116.33	(60)
10.00	81.34	(52)	116.35[b]	(60)
12.00	95.56	(84)	98.53	(67)
16.00	84.78[b]	(67)	66.27	(71)
20.00	31.41	(88)	27.69	(79)
24.00	11.00	(129)	7.28[b]	(142)
30.00	1.85	(600)	0	
36.00	0		0	
AUC_{0-t} (ng*hr/mL)	2408.9	(44)	2359.5	(44)
AUC_{0-inf} (ng*hr/mL)	2733.3[d]	(44)	2547.1[c]	(43)
C_{max} (ng/mL)	287.40	(37)	255.86	(37)
$LNAUC_{0-t}$	2188.7[e]	(49)	2154.0[e]	(47)
$LNAUC_{0-inf}$	2476.6[d,e]	(52)	2328.2[c,e]	(47)
LNC_{max}	267.34[e]	(42)	236.07[e]	(45)
T_{max} (hour)	2.51	(70)	2.56	(36)
$T_{1/2}$ (hour)	3.90	(55)	4.17	(41)

a = unless otherwise indicated: b = (n=35), c = (n=31), d = (n=24)
e = geometric mean

Table 6: Mean (C.V.%) Plasma M5 Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 36[a] - 400 mg ER Tablet - Fasting Study)

Time (hour)	Purepac (Treatment A)		Hoechst-Roussel (Treatment B)	
0	0		0	
0.33	208.13	(67)	174.19	(55)

0.67	513.02 (33)	465.68 (38)
1.00	641.65 (28)	563.50[a] (30)
1.50	693.54 (28)	621.04 (25)
2.00	692.50 (28)	607.99 (28)
2.50	655.92 (29)	583.40[a] (28)
3.00	610.46 (27)	568.78 (31)
3.50	569.05 (27)	535.61 (32)
4.00	497.18 (28)	502.40 (30)
4.50	432.43 (27)	454.70 (26)
5.00	378.00 (29)	395.28 (24)
6.00	303.53 (33)	331.48 (35)
8.00	243.91 (37)	308.32[a] (40)
10.00	196.61 (47)	282.04[b] (42)
12.00	205.58 (58)	215.73 (39)
16.00	187.55[b] (53)	153.40 (52)
20.00	76.99 (84)	73.58 (73)
24.00	28.87 (121)	24.34[b] (113)
30.00	0	0
36.00	0	0
AUC_{0-t} (ng*hr/mL)	5893.7 (22)	5926.0 (23)
AUC_{0-inf} (ng*hr/mL)	6171.1[d] (22)	6292.4[c] (23)
C_{max} (ng/mL)	753.76 (24)	679.45 (25)
$LNAUC_{0-t}$	5749.1[e] (23)	5757.7[e] (25)
$LNAUC_{0-inf}$	6008.3[d,e] (25)	6109.6[c,e] (26)
LNC_{max}	731.54[e] (26)	656.21[e] (28)
T_{max} (hour)	1.82 (36)	2.03 (44)
$T_{1/2}$ (hour)	3.85 (74)	3.69 (49)

a = unless otherwise indicated: b = (n=35), c = (n=33), d = (n=29)
e = geometric mean

Analysis of Variance was performed on the untransformed and log-transformed data of AUC_{0-t},

AUC_{0-inf}, and C_{max}, using SAS GLM procedure. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

Significant treatment effects were detected for the following parameters: C_{max} and LNC_{max} of pentoxifylline, C_{max} and LNC_{max} of M1, and C_{max} and LNC_{max} of M5 (p=0.0007 - 0.0191).

Significant sequence effects were detected for the following parameters: AUC_{0-t}, $LNAUC_{0-t}$, C_{max}, and LNC_{max} of M5 (p=0.0524 - 0.0922).

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Tables 7-9.

Table 7: Statistical Analysis of Pentoxifylline Data – Fasting Study – (n=36*)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	472.54	475.41	0.99	(0.913; 1.075)
$LNAUC_{0-t}$	6.0297 (415.58[a])	6.0236 (413.07[a])	1.01[b]	(0.929; 1.090)
AUC_{0-inf}	582.81[d]	609.11[c]	0.96	(0.781; 1.132)
$LNAUC_{0-inf}$	6.2818[d] (534.73[a,d])	6.2900[c] (539.15[a,c])	0.99[b]	(0.879; 1.119)
C_{max}	76.76	68.96	1.11	(1.031; 1.195)
LNC_{max}	4.2610 (70.88[a])	4.1251 (61.87[a])	1.14[b]	(1.058; 1.241)

a = Geometric Mean
b = Ratio of Geometric Means
* = Unless otherwise indicated: c = (n=19), d = (n=13)

Table 8: Statistical Analysis of M1 Data – Fasting Study – (n=36*)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	2408.9	2359.5	1.02	(0.962; 1.080)
$LNAUC_{0-t}$	7.6910 (2188.7[a])	7.6751 (2154.0[a])	1.02[b]	(0.951; 1.086)
AUC_{0-inf}	2580.7[d]	2585.4[c]	1.00	(0.910; 1.086)

$LNAUC_{0\text{-}inf}$	7.7616[d] (2348.5[a,d])	7.7747[c] (2379.7[a,c])	0.99[b]	(0.887; 1.098)
C_{max}	287.40	255.86	1.12	(1.039; 1.208)
LNC_{max}	5.5885 (267.34[a])	5.4641 (236.07[a])	1.13[b]	(1.049; 1.222)

a = Geometric Mean
b = Ratio of Geometric Means
* = Unless otherwise indicated: c = (n=31), d = (n=24)

Table 9: Statistical Analysis of M5 Data – Fasting Study – (n=36*)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
$AUC_{0\text{-}t}$	5893.7	5926.0	0.99	(0.950; 1.039)
$LNAUC_{0\text{-}t}$	8.6568 (5749.1[a])	8.6583 (5757.7[a])	1.00[b]	(0.947; 1.053)
$AUC_{0\text{-}inf}$	6077.6[d]	6263.8[c]	0.97	(0.924; 1.017)
$LNAUC_{0\text{-}inf}$	8.6772[d] (5867.4[a,d])	8.7157[c] (6097.8[a,c])	0.96[b]	(0.911; 1.016)
C_{max}	753.76	679.45	1.11	(1.031; 1.195)
LNC_{max}	6.5951 (731.54[a])	6.4865 (656.20[a])	1.11[b]	(1.052; 1.166)

a = Geometric Mean
b = Ratio of Geometric Means
* = Unless otherwise indicated: c = (n=33), d = (n=29)

Comments:

1. For the data of pentoxifylline, the T_{max} of 7 subjects (#1, 4, 10, 12, 17, 21,& 37) during treatment A and 3 subjects (10, 31, & 33) during treatment B were of the first sampling time point. The C_{max} thus estimated might not be accurate. Therefore, data of these 9 subjects from both treatments were deleted and the statistics rerun by the reviewer. The results are presented below in Table 10.

Table 10: Statistical Analysis of Pentoxifylline Data – Fasting Study – (n=27*) – Excluding 9 Subjects –

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval

AUC_{0-t}	520.28	517.73	1.00	(0.910; 1.100)
$LNAUC_{0-t}$	6.1609 (473.83[a])	6.1472 (467.40[a])	1.01[b]	(0.926; 1.109)
AUC_{0-inf}	677.90[d]	681.27[c]	0.99	(0.778; 1.212)
$LNAUC_{0-inf}$	6.4543[d] (635.42[a,d])	6.4141[c] (610.42[a,c])	1.04[b]	(0.903; 1.200)
C_{max}	81.20	74.21	1.09	(0.999; 1.189)
LNC_{max}	4.3268 (75.70[a])	4.2312 (68.80[a])	1.10[b]	(1.022; 1.197)

a = Geometric Mean
b = Ratio of Geometric Means
* = Unless otherwise indicated: c = (n=14), d = (n=9)

2. The 90% confidence intervals of $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} are all within the limit of 80-125%

3. The calculations of the pharmacokinetic parameters and the 90% confidence intervals have been recalculated and confirmed by the reviewer.

Bioequivalence Study -- Single Dose -- Fed and Fasted -- 3-Way Crossover

The objective of this study was to compare the single-dose bioavailability of Purepac and Hoechst-Roussel (Trental[R]) 400 mg pentoxifylline extended release tablets under fed condition. In addition, the bioavailability of the sponsor's (Purepac's) product was compared under fed and fasted conditions.

The clinical study was conducted at
during 11/30-12/16/95 with as co-principal
investigators. The analytical study was conducted at in
during 12/28/95-01/16/96 by analysts

The design of the study was a single-dose, 3-way crossover of the test and reference products in fed non-smoking male volunteers and the test product in the same volunteers under fasted condition. The protocol and the informed consent form were approved by Institutional Review Board on 11/15/95.

Eighteen non-smoking male volunteers, 18-39 years old, were enrolled. They consisted of 9 Caucasians and 9 African-Americans. Each volunteer completed the screening process within 28 days prior to period 1 dosing. The inclusion and exclusion criteria, and restriction instructions

were the same as those for the fasted study.

Subjects were confined to the clinical facility from 12 hours before to 30 hours after dosing. After an overnight fast, on the morning of 12/01/95, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Pentoxifylline extended-release tablet, 1 x 400 mg, Purepac Pharmaceutical Co., lot #PI-890, potency 100.4%, manufacturing date 09/07/95, lot size of tablets.

Treatment B - Test Drug: Pentoxifylline extended-release tablet, 1 x 400 mg, Purepac Pharmaceutical Co., lot #PI-890, potency 100.4%, manufacturing date 09/07/95, lot size of tablets. given 30 minutes after a standard breakfast*.

Treatment C - Reference Drug: Trental[R] tablet, 1 x 400 mg, Hoechst-Roussel, lot #0781865, expires 05/97, potency 100.5%, given 30 minutes after a standard breakfast*.

* = 1 buttered English muffin, 1 fried egg, 1 slice of America cheese, 1 rasher of Canadian bacon, hash brown potatoes, 180 mL of orange juice and 240 mL of whole milk.

At 7-day intervals, on 12/08/95 and 12/15/95, each subject was crossed over to one of the other treatments according to the treatment sequence of ABC, ACB, BAC, BCA, CAB or CBA. Standard meals were served from 4 hours after dosing. Subjects engaged in normal activity for 4 hours after dosing. Safety monitoring included measurements of body temperature prior to dosing, and vital signs (pulse rate, blood pressure and respiration rate) prior to dosing and at 2 hours after dosing.

Blood samples (10 mL each) were collected in Vacutainers containing EDTA before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, and 30 hours. Plasma samples were prepared, frozen, and stored at -12°C pending shipment to the analytical site. The storage temperature at the analytical site was -22°C.

Each subject received a physical examination following the 30-hour blood draw in period 3.

Analytical Method -- **Not for Release through FOI**:

Results:

Of the 18 subjects enrolled, subject #6 was withdrawn from the study 4.8 hours after period 1 (treatment A) dosing due to poor vein and faint feeling.

Excluding the adverse events reported by subject #6, 14 adverse events were reported by 8 subjects, 5 during treatment A, 1 during treatment B and 8 during treatment C. The complains included pain or bruise at venipuncture site, nosebleed, headache, weak feeling, blurry vision, discolored vein, vomiting, tendinitis, skin cut or scrape.

Some protocol deviations were judged unlikely to affect the bioavailability comparison, i.e., subjects #10 was given 500 mg acetaminophen 10 hours after period 2 dosing to relieve headache; and delay or early blood sampling which were time adjusted in the concentration-time profile, gum-chewing, etc..

All post-study laboratory test and physical examination were normal or judged not clinically significant.

The plasma samples from 17 subjects were assayed for pentoxifylline, M5 and M1. Among the 969 study samples analyzed, reassay was conducted because of anomaly of the original values in 21 samples for M5, 21 for M1, and 52 for pentoxifylline. Each repeated sample was reassayed twice and the median value was reported.

The mean plasma concentrations of M5, M1 and pentoxifylline at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Figures 4-6 and Tables 12-14. The elimination constant used to calculate $AUC_{0\text{-}inf}$ was obtained by linear least-square regression analysis using the last 3 non-zero points. No value of $AUC_{0\text{-}inf}$ or $T_{1/2}$ was reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time

profile. Some concentration values were considered to be pharmacokinetic anomalies, i.e. 6 samples for pentoxifylline, and 2 samples for M1. These values were set to missing for pharmacokinetic and statistical analyses. None of these missing values were near C_{max}.

Table 12: Mean (C.V.%) Plasma Pentoxifylline Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 17[a] - 400 mg ER Tablet - Fed and Fasted Study)

Time (hour)	Purepac - Fasted (Treatment A)	Purepac - Fed (Treatment B)	Hoechst-Roussel - Fed (Treatment C)
0	0	0	0
0.5	34.46 (55)	9.71 (106)	12.98 (135)
1.0	55.96 (67)	40.42 (91)	36.17 (86)
1.5	52.15 (58)	52.68 (82)	59.52 (82)
2.0	46.30 (67)	81.17 (110)	71.08 (115)
2.5	43.91 (59)	113.01 (88)	99.09 (88)
3.0	36.36 (57)	89.97 (63)	93.61 (71)
3.5	35.70 (60)	84.21 (55)	76.95 (60)
4.0	30.25[b] (45)	82.30 (57)	94.47 (66)
4.5	45.22 (54)	137.34 (64)	113.89 (54)
5.0	33.15 (67)	92.92 (58)	82.59 (71)
6.0	24.16[b] (56)	65.07 (58)	70.28 (72)
8.0	19.34 (68)	33.72[b] (78)	34.64 (62)
10.0	17.62 (80)	51.79 (196)	29.73 (82)
12.0	24.94[b] (100)	11.62 (129)	15.43 (107)
16.0	19.37[c] (87)	0	4.66 (134)
20.0	3.62 (151)	0	0
24.0	0.42[b] (400)	0	0
30.0	0.46 (412)	0	0
AUC_{0-t} (ng*hr/mL)	459.9 (58)	686.2 (58)	668.3 (51)
AUC_{0-inf} (ng*hr/mL)	698.8[e] (49)	824.0[d] (35)	790.9[e] (39)
C_{max} (ng/mL)	70.78 (38)	190.68 (63)	158.70 (56)
LNAUC$_{0-t}$	359.4[f] (100)	572.7[f] (75)	572.1[f] (70)

$LNAUC_{0-\infty}$	630.0[e,f] (58)	749.5[d,f] (58)	730.6[e,f] (45)
LNC_{max}	58.98[f] (78)	154.69[f] (79)	131.00[f] (81)
T_{max} (hour)	2.21 (127)	4.21 (41)	4.32 (43)
$T_{1/2}$ (hour)	11.96 (150)	1.50[d] (44)	2.69[e] (50)

a = unless otherwise indicated: b = (n=16), c = (n=14), d = (n=8), e = (n=4)
f = geometric mean

Table 13: Mean (C.V.%) Plasma M1 Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 17- 400 mg ER Tablet - Fed and Fasted Study)

Time (hour)	Purepac - Fasted (Treatment A)	Purepac - Fed (Treatment B)	Hoechst-Roussel - Fed (Treatment C)
0	0	0	0
0.5	64.75 (61)	12.47 (109)	16.75 (169)
1.0	183.07 (54)	77.69 (84)	67.83 (75)
1.5	229.29 (50)	148.99 (77)	143.31 (62)
2.0	252.04 (48)	200.82 (68)	203.28 (80)
2.5	254.92 (50)	311.81 (88)	280.22 (82)
3.0	241.55 (50)	371.67 (78)	329.73 (70)
3.5	213.17 (50)	381.93 (57)	364.49 (59)
4.0	202.07 (50)	421.21 (55)	397.29 (55)
4.5	171.57 (47)	438.43 (52)	410.47 (54)
5.0	161.94 (50)	403.04 (55)	369.40 (54)
6.0	121.15 (55)	305.41 (48)	301.49 (67)
8.0	88.66 (46)	176.43 (73)	200.38 (67)
10.0	78.34[b] (53)	187.48 (112)	133.72 (68)
12.0	92.75[b] (78)	86.90 (113)	87.54 (82)
16.0	91.00 (72)	7.60 (154)	34.33 (110)
20.0	34.96 (76)	0	8.27 (150)
24.0	12.05 (100)	0	1.07 (412)
30.0	3.27 (339)	0	0
AUC_{0-t} (ng*hr/mL)	2328.4 (50)	2893.3 (47)	2885.7 (47)

AUC_{0-inf} (ng*hr/mL)	2687.6[e] (37)	3199.8[d] (33)	3131.4[e] (44)
C_{max} (ng/mL)	271.74 (48)	556.63 (55)	475.61 (49)
$LNAUC_{0-t}$	1938.3[f] (82)	2503.8[f] (68)	2487.5[f] (71)
$LNAUC_{0-inf}$	2525.8[e,f] (39)	3006.2[d,f] (41)	2735.4[e,f] (69)
LNC_{max}	230.47[f] (77)	469.90[f] (74)	411.16[f] (71)
T_{max} (hour)	2.15 (24)	5.35 (44)	5.33 (41)
$T_{1/2}$ (hour)	3.97[e] (44)	1.59[d] (32)	2.78[e] (57)

a = unless otherwise indicated: b = (n=16), c = (n=15), d = (n=12), e = (n=11)
f = geometric mean

Table 14: Mean (C.V.%) Plasma M5 Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 17- 400 mg ER Tablet - Fed and Fasted Study)

Time (hour)	Purepac - Fasted (Treatment A)	Purepac - Fed (Treatment B)	Hoechst-Roussel - Fed (Treatment C)
0	0	0	0
0.5	277.41 (39)	45.40 (105)	57.68 (110)
1.0	575.23 (23)	226.93 (80)	198.44 (64)
1.5	613.43 (21)	346.90 (59)	331.24 (46)
2.0	624.08 (27)	438.18 (41)	397.38 (55)
2.5	592.91 (32)	563.11 (40)	506.49 (51)
3.0	528.65 (35)	667.54 (38)	613.81 (47)
3.5	474.35 (35)	693.42 (32)	654.82 (43)
4.0	437.71 (36)	753.56 (35)	715.94 (40)
4.5	375.80 (33)	773.26 (37)	706.14 (33)
5.0	333.51 (36)	669.25 (33)	593.87 (30)
6.0	256.05 (45)	558.37 (43)	497.28 (45)
8.0	202.95 (29)	326.69 (66)	362.10 (51)
10.0	161.17 (40)	323.50 (80)	256.15 (71)
12.0	187.25 (50)	133.07 (86)	165.30 (65)
16.0	196.35 (53)	9.43 (168)	57.51 (94)
20.0	76.12 (71)	0	16.24 (162)
24.0	24.92 (106)	0	1.78 (412)

30.0	3.81 (412)	0	0
AUC_{0-t} (ng*hr/mL)	5286.0 (22)	5206.2 (21)	5210.6 (20)
AUC_{0-inf} (ng*hr/mL)	5510.9[d] (20)	5353.9[e] (23)	5482.8[b] (18)
C_{max} (ng/mL)	684.14 (25)	905.03 (28)	833.72 (33)
$LNAUC_{0-t}$	5174.3[f] (21)	5110.3[f] (19)	5122.6[f] (19)
$LNAUC_{0-inf}$	5416.2[d,f] (19)	5240.3[e,f] (21)	5403.4[b,f] (17)
LNC_{max}	666.32[f] (23)	874.55[f] (27)	795.30[f] (32)
T_{max} (hour)	1.62 (40)	4.94 (42)	4.78 (43)
$T_{1/2}$ (hour)	3.35[d] (37)	1.41[e] (31)	2.61[b] (51)

a = unless otherwise indicated: b = (n=16), c = (n=13), d = (n=12)
f = geometric mean

Analysis of Variance was performed on the untransformed and log-transformed data of AUC_{0-t}, AUC_{0-inf}, and C_{max}, using SAS GLM procedure. The model included subjects, period, treatment and first-order carryover as factors. The LS means of the non-transformed and log-transformed pharmacokinetic parameters and ratios of these means are presented in Tables 15-17.

Table 15: Ratios of Least-Square Means of Pharmacokinetic Parameters of Pentoxifylline Fed and Fasted Study (n=17)

Parameter	LS Means -- Purepac Fasted -- Treatment A --	LS Means -- Purepac Fed -- Treatment B --	LS Means -- Hoechst-R. Fed -- Treatment C --	B/C	B/A
AUC_{0-t}	473.7	677.7	663.0	1.02	1.43
$LNAUC_{0-t}$	5.8756 (356.2[a])	6.3192 (555.1[a])	6.3894 (595.5[a])	0.93[b]	1.56[b]
AUC_{0-inf}	585.1[a]	657.5[d]	756.9[c]	0.87	1.12
$LNAUC_{0-inf}$	6.2881[a] (538.1[a,a])	6.4044[d] (604.5[a,d])	6.5186[c] (677.6[a,c])	0.89[b]	1.12[b]
C_{max}	76.70	194.72	148.74	1.31	2.54
LNC_{max}	4.0705 (58.58[a])	5.0419 (154.76[a])	4.8815 (131.83[a])	1.17[a]	2.64[b]
T_{max}	2.42	3.93	4.38	0.90	1.62

$T_{1/2}$	8.65[e]	3.69[d]	2.32[c]	1.59	0.43

* = unless otherwise indicated: c = (n=14), d = (n=8), e = (n=4)
a = Geometric Mean
b = Ratio of Geometric Means

Table 16: Ratios of Least-Square Means of Pharmacokinetic Parameters of M1 Fed and Fasted Study (n=17)

Parameter	LS Means -- Purepac Fasted -- Treatment A --	LS Means -- Purepac Fed -- Treatment B --	LS Means -- Hoechst-R. Fed -- Treatment C --	B/C	B/A
AUC_{0-t}	2330.0	2875.2	2902.2	0.99	1.23
$LNAUC_{0-t}$	7.5524 (1905.2[a])	7.8177 (2484.1[a])	7.8441 (2550.7[a])	0.97[b]	1.30[b]
AUC_{0-inf}	2320.4[e]	2901.3[d]	3030.9[c]	0.96	1.25
$LNAUC_{0-inf}$	7.6161[e] (2030.7[a,e])	7.8441[d] (2550.5[a,d])	7.8830[c] (2651.9[a,c])	0.96[b]	1.26[b]
C_{max}	284.84	568.24	450.90	1.26	1.99
LNC_{max}	5.4409 (230.64[a])	6.1600 (473.42[a])	6.0108 (407.80[a])	1.16[b]	2.05[b]
T_{max}	2.38	5.36	5.08	1.05	2.25
$T_{1/2}$	4.10[e]	1.33[d]	2.60[c]	0.51	0.32

* = unless otherwise indicated: c = (n=15), d = (n=12), e = (n=11)
a = Geometric Mean
b = Ratio of Geometric Means

Table 17: Ratios of Least-Square Means of Pharmacokinetic Parameters of M5 Fed and Fasted Study

Parameter	LS Means -- Purepac Fasted -- Treatment A --	LS Means -- Purepac Fed -- Treatment B --	LS Means -- Hoechst-R. Fed -- Treatment C --	B/C	B/A
AUC_{0-t}	5257.0	5223.0	5222.7	1.00	0.99
$LNAUC_{0-t}$	8.5452 (5141.9[a])	8.5403 (5117.0[a])	8.5464 (5148.1[a])	0.99[b]	0.99[b]
AUC_{0-inf}	5414.8[e]	5377.8[d]	5474.2[c]	0.86	0.99
$LNAUC_{0-inf}$	8.5791[e] (5319.3[a,e])	8.5705[d] (5273.9[a,d])	8.5958[c] (5409.2[a,c])	0.97[b]	0.99[b]

C_{max}	675.33	914.98	832.58	1.10	1.35
LNC_{max}	6.4965 (662.83[a])	6.7800 (880.09[a])	6.6776 (794.44[a])	1.11[b]	1.33[b]
T_{max}	1.85	5.08	4.40	1.15	2.75
$T_{1/2}$	3.34[a]	1.22[d]	2.67[e]	0.46	0.36

* = unless otherwise indicated: c = (n=16), d = (n=13), e = (n=12)
a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. For the data of pentoxifylline, the T_{max} of 4 subjects during treatment A were of the first sampling time point. The C_{max} thus estimated may not be accurate. Therefore, data of these 4 subjects (#1, 3, 4, and 7) during treatment A were deleted and the statistics rerun by the reviewer. The results are presented below in Table 18.

Table 18: Ratios of Least-Square Means of Pharmacokinetic Parameters of Pentoxifylline Fed and Fasted Study (n=17[c]) – 4 Subjects Excluded for Treatment A

Parameter	LS Means – Purepac Fasted – Treatment A –	LS Means – Purepac Fed – Treatment B –	LS Means – Hoechst-R. Fed – Treatment C –	B/C	B/A
AUC_{0-t}	420.21[d]	685.58	674.79	1.02	1.63
$LNAUC_{0-t}$	5.9913[d] (399.92[a,d])	6.3460 (570.12[a])	6.3529 (574.14[a])	0.99[b]	1.42[b]
AUC_{0-inf}	585.1[f]	657.5[e]	756.9[e]	0.87	1.12
$LNAUC_{0-inf}$	6.2881[f] (538.1[a,f])	6.4044[e] (604.5[a,e])	6.5186[e] (677.6[a,e])	0.89[b]	1.12[b]
C_{max}	50.69[d]	189.05	159.31	1.19	3.73
LNC_{max}	4.1450[d] (63.12[a,d])	5.0368 (153.97[a])	4.8833 (132.07[a])	1.17[b]	2.44[b]

* = unless otherwise indicated: c = (n=14), d = (n=13), e = (n=8), f = (n=4)
a = Geometric Mean
b = Ratio of Geometric Means

2. The ratios of least-square geometric means of AUC_{0-t}, AUC_{0-inf} and C_{max} are all within 0.8-1.25 for pentoxifylline, M1 and M5.

3. The effect of food on the bioavailability of sponsor's pentoxifylline 400 mg extended-release tablet was different than that of immediate-release dosage at previously reported (see Introduction).

When comparing post-prandial to fasting administration of the test drug, the mean C_{max} of pentoxifylline and both metabolites, M1 and M5, were 1.3-2.6 times; the mean AUCs of pentoxifylline and M1 were 1.1-1.6 times; and the mean T_{max} of pentoxifylline and both metabolites were increase by 1.5-3.2 hours; .

Bioequivalence Study -- Multiple Dose -- Fasted -- 2-Way Crossover

The objective of this study was to compare the steady state bioavailability of Purepac and Hoechst-Roussel (Trental[R]) 400 mg pentoxifylline extended release tablets under fasted condition.

The clinical study was conducted at during 11/28-12/02/95 and 12/12-12/16/95 with as co-principal investigators. The analytical study was conducted at during 12/27/95-01/25/96 by analysts

The design of the study was a multiple-dose (3 doses per day at 7 am, 3 pm and 11 pm, for 3 days and 1 dose at 7 am on the 4th day), 2-way crossover in fasting non-smoking male volunteers. The protocol and the informed consent form were approved by Institutional Review Board on 11/15/95.

Thirty-eight (36 plus 2 alternates) non-smoking male volunteers, 19-45 years old, were enrolled. They consisted of 21 Caucasian and 17 African-Americans. Each volunteer completed the screening process within 28 days prior to period 1 dosing. The inclusion and exclusion criteria, and restriction instructions were the same as those for the fasted study.

Subjects were confined to the clinical facility from 12 hours before the first dose to 8 hours after the last dose on day 4. A standard meal was served 10 hours prior to the first dose and after an overnight fast of 10 hr, at 7 am of 11/29/95, each subject received one of the following treatments:

Treatment A - Test Drug:	Pentoxifylline extended-release tablet, 1 x 400 mg, 3 times a day (at 7 am, 3 pm and 11 pm) for 3 days and 1 time on the 4th day, Purepac Pharmaceutical Co., lot #PI-890, potency 100.4%, manufacturing date 09/07/95, lot size of tablets.
Treatment B - Reference Drug:	Trental[R] tablet, 1 x 400 mg, 3 times (at 7 am, 3 pm and 11 pm) a day for 3 days and 1 time on the 4th

day, Hoechst-Roussel, lot #0781865, expires 05/97, potency 100.5%.

After an 11-day washout from the last dose, on 12/13/95, each subject was crossed over to the alternative treatment. Subjects were required to fast overnight prior to, and for 4 hours after each morning dose, and for 2 hours prior to and following each subsequent dose.

Safety monitoring (pulse, blood pressure and respiration) was conducted prior to and at 2 hours after the morning dose, prior to each subsequent dose, and at 2 hours after the last dose on the 4th day. Body temperature was only recorded before initial dosing on day 1 of each period.

Blood samples (10 mL each) were collected in Vacutainers containing EDTA before initial dosing on day 1, before first dose on days 2, 3, and 4, and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, and 8 hours after the dose on day 4. Plasma samples were prepared, frozen, and stored at -12°C pending shipment to the analytical site. The storage temperature at the analytical site was -22°C.

Each subject received a physical examination following the 8-hour blood draw on day 4 in period 2.

Analytical Method -- **Not for Release through FOI**:

Results:

Of the 38 subjects enrolled, 5 did not complete the study. Subject #3 withdrew from the study 7.6 hours after dose 6 in period 2 for personal reason and # 29 due to back injury sustained during the washout period. Subject #11 withdrew from the study due to adverse events not related to study drug or procedure. Subjects # 6 and #36 were withdrawn from the study due to adverse reactions (stomach pain, nausea, vomiting, cold, diaphoretic extremities, headache) judged possibly related to the study drug.

Excluding the 5 subjects who did not complete the study, 32 adverse events were reported by 14 subjects, 15 events during treatment A and 17 during treatment B. The adverse events were vomiting, headache, sore throat, cough, nervousness, lower back pain, hyper feeling, stomach pain, bruise at elbow, runny nose, cold feeling, lightheaded feeling, blurry eyesight, nausea, and insomnia.

Some protocol deviations were judged unlikely to affect the bioavailability comparison, i.e., delay or early blood sampling which were time adjusted in the concentration-time profile, meal schedule deviations and subject #19 took 12x1 tablespoon of cough syrup (strength and formulation not specified) 6-8 days after dose 10 in period 1 to alleviate a moderate cough..

All post-study laboratory test and physical examination were normal or judged not clinically significant.

The plasma samples from 33 subjects were assayed for pentoxifylline, M5 and M1. Among the 1122 study samples analyzed, the number of sample reassayed due to anomaly of the original values were 7 for pentoxifylline and 2 for M1. Each repeated sample was reassayed twice and the median value reported.

The mean plasma concentrations of pentoxifylline, M1 and M5 at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Figures 7-9 and Tables 20-22. Pharmacokinetic parameters include:

- $AUC_{72-\tau}$,
- C_{max} (maximum concentration over the final dosing interval),
- C_{min} (minimum concentration over the final dosing interval),
- T_{max} (time of C_{max} after the last dose),
- Css_{av} calculated as ($AUC_{72-\tau}/\tau$), and
- percentage of fluctuation (Flux) calculated as $[(C_{max}-C_{min})/Css_{av}]x100$.

Table 20: Mean (C.V.%) Plasma Pentoxifylline Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 33 - 400 mg ER Tablet - Multiple Dose - Fasting Study)

Time (hour)	Purepac (Treatment A)	Hoechst-Roussel (Treatment B)
0	0	0
24.00	92.91 (148)	73.99 (77)
48.00	78.60 (71)	79.84 (67)
72.00	61.85 (65)	58.36 (65)
72.33	103.74 (61)	107.74 (69)
72.67	140.99 (46)	137.78 (59)
73.00	136.75 (50)	116.65 (50)
73.50	116.68 (46)	113.65 (49)
74.00	104.43 (54)	103.47 (50)
74.50	99.39 (62)	93.83 (54)
75.00	90.73 (55)	93.71 (55)
75.50	85.15 (59)	84.64 (54)
76.00	72.91 (53)	72.76 (56)
76.50	92.04 (59)	102.58 (58)
77.00	93.96 (67)	99.43 (56)
78.00	68.80 (72)	77.53 (61)
80.00	42.93 (65)	55.50 (65)
$AUC_{0-\tau}$ (ng*hr/mL)	695.9 (51)	714.0 (51)
C_{max} (ng/mL)	163.42 (41)	158.71 (52)
C_{min} (ng/mL)	36.58 (70)	43.42 (54)
$LNAUC_{0-\tau}$	622.4[a] (50)	642.1[a] (48)
LNC_{max}	149.86[a] (45)	142.36[a] (51)
T_{max} (hour)	1.59 (88)	1.58 (93)
Css_{av} (ng/mL)	86.99 (51)	89.25 (51)
Flux (%)	157.24 (35)	131.93 (29)

a = geometric mean

Table 21: Mean (C.V.%) Plasma M1 Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 33 - 400 mg ER Tablet - Multiple Dose - Fasting Study)

Time (hour)	Purepac (Treatment A)		Hoechst-Roussel (Treatment B)	
0	0		0	
24.00	386.45	(93)	389.58	(77)
48.00	408.51	(71)	382.59	(58)
72.00	311.95	(59)	303.28	(65)
72.33	352.40	(56)	340.42	(61)
72.67	465.01	(47)	457.01	(58)
73.00	530.80	(43)	502.92	(53)
73.50	544.77	(41)	528.21	(54)
74.00	544.10	(42)	536.03	(54)
74.50	525.06	(44)	531.07	(55)
75.00	506.31	(48)	510.17	(58)
75.50	483.94	(51)	476.67	(55)
76.00	436.64	(54)	453.57	(55)
76.50	390.74	(57)	395.46	(54)
77.00	361.14	(60)	390.21	(52)
78.00	286.94	(60)	316.32	(53)
80.00	183.91	(55)	232.17	(57)
$AUC_{ss,\tau}$ (ng*hr/mL)	3146.7	(47)	3225.6	(53)
C_{max} (ng/mL)	599.38	(42)	571.26	(52)
C_{min} (ng/mL)	174.03	(60)	217.94	(60)
$LNAUC_{ss,\tau}$	2845.76[a]	(49)	2894.43[a]	(48)
LNC_{ss}	544.39[a]	(49)	513.56[a]	(48)
T_{max} (hour)	2.033	(53)	2.127	(45)
$Css_{,v}$ (ng/mL)	393.3	(47)	403.2	(53)
Flux (%)	110.81	(30)	89.20	(25)

a = geometric mean

Table 22: Mean (C.V.%) Plasma M5 Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 33 - 400 mg ER Tablet - Multiple Dose - Fasting Study)

Time (hour)	Purepac (Treatment A)	Hoechst-Roussel (Treatment B)
0	0	0
24.00	652.29 (57)	671.20 (31)
48.00	728.10 (38)	712.63 (28)
72.00	623.67 (47)	587.67 (36)
72.33	707.63 (40)	662.73 (29)
72.67	953.92 (29)	899.58 (27)
73.00	1047.54 (26)	956.59 (24)
73.50	1034.40 (22)	970.55 (25)
74.00	965.51 (19)	942.73 (26)
74.50	887.17 (19)	901.05 (25)
75.00	855.85 (22)	864.44 (25)
75.50	817.18 (22)	804.06 (26)
76.00	743.01 (21)	738.18 (25)
76.50	688.25 (22)	697.68 (24)
77.00	643.27 (26)	676.46 (26)
78.00	529.25 (29)	585.60 (26)
80.00	352.44 (32)	439.97 (35)
AUC_{0-t} (ng*hr/mL)	5718.6 (18)	5771.3 (21)
C_{max} (ng/mL)	1119.18 (24)	1040.54 (23)
C_{min} (ng/mL)	328.50 (30)	415.23 (32)
$LNAUC_{0-t}$	5624.09[a] (19)	5650.70[a] (21)
LNC_{max}	1088.66[a] (49)	1016.89[a] (48)
T_{max} (hour)	1.411 (48)	1.451 (51)
Css_{av} (ng/mL)	714.8 (18)	721.4 (21)
Flux (%)	110.29 (26)	87.18 (26)

a = geometric mean

Analysis of Variance was performed on the untransformed and log-transformed data of AUC_{0-t},

$AUC_{0\text{-}inf}$, and C_{max}, using SAS GLM procedure. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

No significant effects ($p<0.05$) were detected for any of the pharmacokinetic parameters of all 3 analytes.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Tables 23-25.

Table 23: Statistical Analysis of Pentoxifylline Data - Multiple Dose - Fasting Study (n = 33)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	695.4	713.5	0.97	(0.909; 1.040)
$LNAUC_{0-t}$	6.4333 (622.21[a])	6.4648 (642.16[a])	0.97[b]	(0.905; 1.038)
C_{max}	163.23	158.53	1.03	(0.935; 1.124)
LNC_{max}	5.0093 (149.81[a])	4.9575 (142.23[a])	1.05[b]	(0.964; 1.151)

a = Geometric Mean
b = Ratio of Geometric Means

Table 24: Statistical Analysis of M1 Data -- Multiple Dose -- Fasting Study (n = 33)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	3148.0	3221.4	0.98	(0.913; 1.041)
$LNAUC_{0-t}$	7.9533 (2844.9[a])	7.9693 (2891.0[a])	0.98[b]	(0.922; 1.050)
C_{max}	599.24	570.33	1.05	(0.958; 1.143)
LNC_{max}	6.2990 (544.02[a])	6.2395 (512.58[a])	1.06[b]	(0.969; 1.163)

a = Geometric Mean
b = Ratio of Geometric Means

Table 25: Statistical Analysis of M5 Data – Multiple Dose – Fasting Study
(n = 33)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	5716.3	5774.5	0.99	(0.946; 1.034)
$LNAUC_{0-t}$	8.6342 (5620.9[a])	8.6400 (5653.4[a])	0.99[b]	(0.953; 1.037)
C_{max}	1118.72	1040.58	1.07	(1.007; 1.144)
LNC_{max}	6.9475 (1087.84[a])	6.9688 (1016.77[a])	1.07[b]	(1.009; 1.135)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. For the data of pentoxifylline, the T_{max} of 3 subjects (#22, 33, & 34) during treatment A and 5 subjects (#4, 5, 12, 30, & 33) during treatment B were of the first sampling time point. The C_{max} thus estimated may not be accurate. Therefore, data of these 7 subjects from both treatments were deleted and the statistics rerun by the reviewer. The results are presented below in Table 26.

Table 26: Statistical Analysis of Pentoxifylline Data - Multiple Dose - Fasting Study
(n = 26)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	740.70	733.33	1.01	(0.905; 1.017)
$LNAUC_{0-t}$	6.4274 (618.57[a])	6.5005 (665.45[a])	0.93[b]	(0.875; 0.987)
C_{max}	161.39	158.62	1.03	(0.942; 1.146)
LNC_{max}	4.9868 (146.46[a])	4.9398 (139.74[a])	1.05[b]	(0.946; 1.161)

a = Geometric Mean
b = Ratio of Geometric Means

2. The 90% confidence intervals of $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} are all within the limit of 80-125%

3. The calculations of the pharmacokinetic parameters and the 90% confidence intervals have been recalculated and confirmed by the reviewer.

General Comment:

The results of all 3 studies are acceptable.

Dissolution Testing:

The dissolution profile of the test and reference drug used in the above bioequivalence studies were investigated using USP apparatus 2 (paddle) in water at 25, 50, 75 and 100 rpm; and in 0.1N HCl, 0.05M, pH 4.0 citrate buffer, 0.05M, pH 6.2 phosphate buffer and 0.05M, pH 7.4 buffer, all at 50 rpm. The sampling time was hourly for 20 hours.

The result of these studies showed that for the test product, the rank order of the dissolution rate was water>0.1N HCl>pH 4.0>pH 6.2>pH 7.4, while that for the reference product was pH 4.0>water>0.1N HCl>pH 6.2>pH 7.4. Water was selected as the dissolution media for routine testing, since pentoxifylline is soluble in water (77 mg/mL) .

The effect of rotation speed in the dissolution profile was slight and 50 rpm was selected.

The specifications chosen to control the dissolution rate are as follows:

Time (Hour)	% Label Claim Released
1	NMT
3	
8	
18	NLT

The comparative dissolution profile of the test and reference products are presented below in Table 27:

Table 27 - In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
Dosage Form: Extended Release Tablet
Dose Strength: 400 mg
ANDA No.: 74-878
Firm: Purepac Pharmaceutical Co.
Submission Date: 3/29/96

I. Conditions for Dissolution Testing:

Composition of Pentoxifylline 400 mg Extended-Release Tablet by Purepac (--Not Releasable through FOI--)

Components	mg/Tablet
Tablet Core:	
Pentoxifylline	400
Hydroxypropyl Methylcellulose	
Providone	
Purified Water	
Talc	
Magnesium Stearate	
Film coating	
Purified Water	
Yellow	
Clear	
Total Tablet Weight	588

* = This component does not appear in significant quantity in the finished product.

Recommendation:

1. The single-dose, fasted bioequivalence study, single-dose, fed and fasted bioequivalence study, and multiple-dose fasted bioequivalence study, conducted by Purepac Pharmaceutical Co. on its Pentoxifylline Extended Release 400 mg Tablet, lot #PI-890, comparing it to Trental[R] 400 mg Tablet, lot #0781865, have been found acceptable by the Division of Bioequivalence.

2. The dissolution testings conducted by Purepac Pharmaceutical Co. on its Pentoxifylline Extended Release 400 mg Tablet has been found acceptable. The firm should provide the dissolution testings data on three manufactured batches of the products in the future.

3. The firm's proposed interim dissolution testings should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 ml
Tolerance: NMT at 1 hour
% at 3 hours
% at 8 hours
NLT % at 18 hours
Reference Drug: Trental[R] (Hoechst-Roussel)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # PI-890 Strength (mg): 400			Reference Product Lot # 0781865 Strength (mg): 400		
	Mean %	Range	%CV	Mean %	Range	%CV
1	17.1		1.2	15.3		1.6
2	27.4		1.0	24.3		1.1
3	35.5		0.9	31.8		1.0
4	42.5		0.9	38.5		1.0
5	48.7		0.9	44.6		1.0
6	54.4		1.0	50.2		1.0
7	59.6		1.0	55.4		1.1
8	64.4		1.0	60.4		1.0
9	68.9		1.0	65.1		1.1
10	73.0		1.1	69.4		1.1
11	76.9		1.0	73.5		1.1
12	80.3		0.9	77.3		1.0
13	83.6		0.9	80.8		1.0
14	86.4		0.9	84.1		1.0
15	88.8		0.9	87.0		0.9
16	91.3		0.8	89.7		0.9
17	93.1		1.0	92.1		0.8
18	94.7		0.9	94.2		0.7
19	96.4		0.9	96.0		0.7
20	97.4		1.0	97.6		0.6

Content uniformity:
test product: 102.2%, range of and CV of 1.3%
reference product: [illegible]

The firm also submitted the comparative drug release profiles in support of its alternate active raw material source. The results are presented below in Table 28:

Table 28 - In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
Dosage Form: Extended Release Tablet
Dose Strength: 400 mg
ANDA No.: 74-878
Firm: Purepac Pharmaceutical Co.
Submission Date: 3/29/96

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 ml
Tolerance: NMT at 1 hour
at 3 hours
% at 8 hours
NLT % at 18 hours
Reference Drug: Trental[R] (Hoechst-Roussel)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # PI-904 Strength (mg): 400			Reference Product Lot # 0781865 Strength (mg): 400		
	Mean %	Range	%CV	Mean %	Range	%CV
1	17.6		2.9	15.3		1.6
2	27.7		2.7	24.3		1.1
3	35.8		2.6	31.8		1.0
4	42.7		2.6	38.5		1.0
5	49.0		2.7	44.6		1.0
6	54.6		2.7	50.2		1.0
7	59.9		2.5	55.4		1.1
8	64.8		2.5	60.4		1.0
9	69.3		2.4	65.1		1.1
10	73.4		2.4	69.4		1.1

11	77.3			2.4	73.5		1.1
12	80.8			2.4	77.3		1.0
13	84.0			2.3	80.8		1.0
14	86.9			2.2	84.1		1.0
15	89.5			2.1	87.0		0.9
16	91.8			2.0	89.7		0.9
17	93.8			2.1	92.1		0.8
18	**95.4**			**2.0**	**94.2**		**0.7**
19	96.9			2.0	96.0		0.7
20	98.1			2.0	97.6		0.6
Content uniformity: test product: 100.4%, range of and CV of 1.4% reference product: 100.8%, range of CV of 0.7%							

Comment:

1. The dissolution tests conducted above complied with the *IN VITRO* requirements of *"Guidance: Pentoxifylline Extended Release Tablets, In Vivo bioequivalence and In Vitro Dissolution Testing"*, published by the Office on 12/22/95.

2. The results indicated that the dissolution profile of the test and reference products in water using USP paddle apparatus at 50 rpm are comparable.

3. The percent dissolved up to 4 hours did not display any dose dumping.

4. The time when of the drug is released was about 12-13 hours.

5. The dissolution testing method and specification for the reference drug, Trental^{R}, are as following (NDA #18631):

   Using USP paddle apparatus in 900 mL of water at 100 rpm, the amount dissolved should be:

Time	% Dissolved
1 hr	
4 hr	
8 hr	
12 hr	

in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

"NMT ' at 1 hour. at 3 hours. at 8 hours. NLT at 18 hours. of the label amount of pentoxifylline are dissolved"

The firm should be informed of the Recommendations.

10/23/96

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG 10/24/96

Concur _____ Date: 10/28/96
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA #74-878 (original, duplicate), Chuang, HFD652 (Huang), Drug File, Division File.

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Final Pink, LWC, 10/23/96 x:\new\firmsnz\purepac\ltrs&rev\74-878sd.396

Figure 1

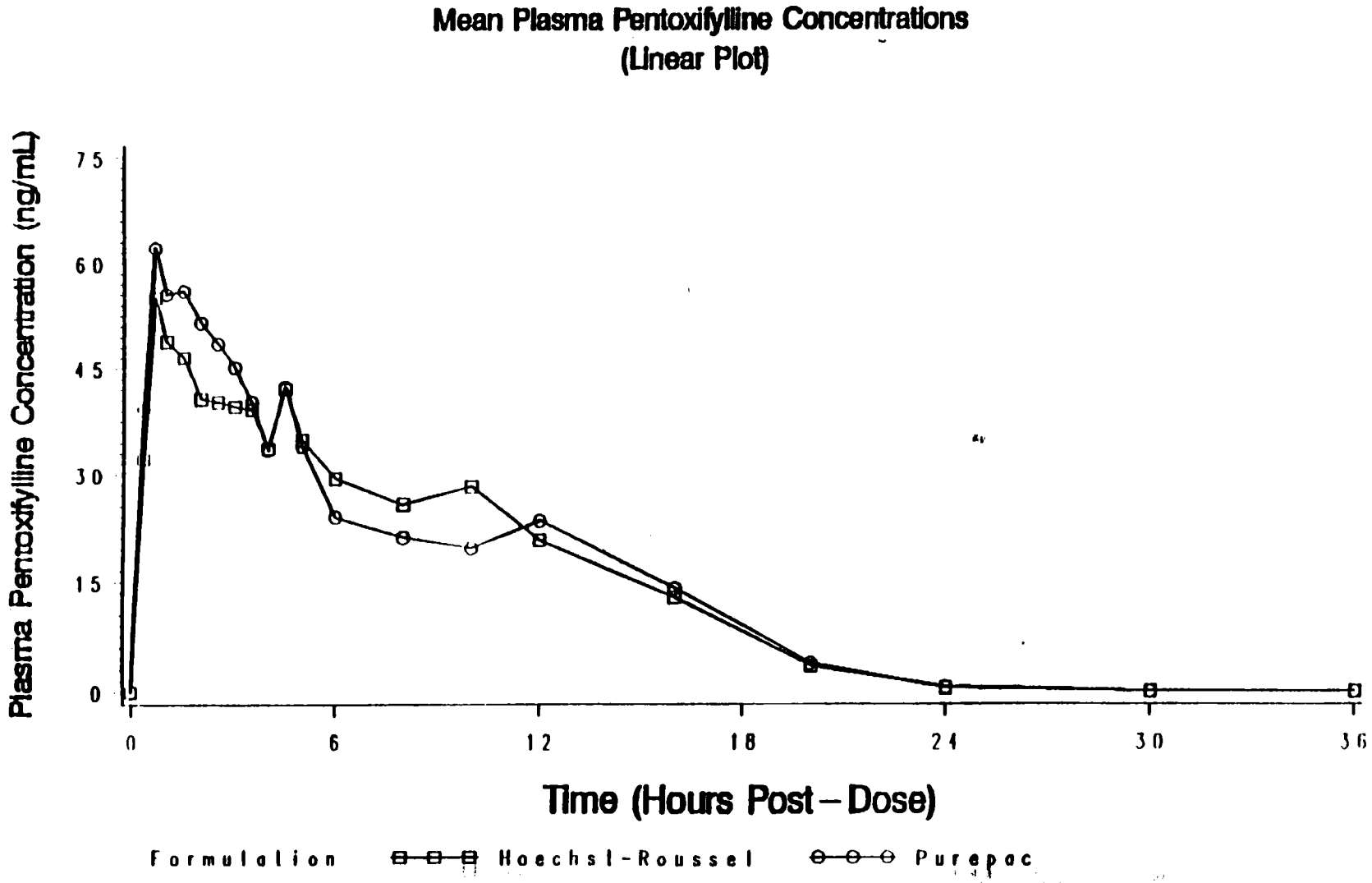
Mean Plasma Pentoxifylline Concentrations
(Linear Plot)
Plasma Pentoxifylline Concentration (ng/mL)
75
60
45
30
15
0
0
6
12
18
24
30
36
Time (Hours Post-Dose)
Formulation
Hoechst-Roussel
Purepac

Figure 2

Mean Plasma Metabolite 1 Concentrations
(Linear Plot)

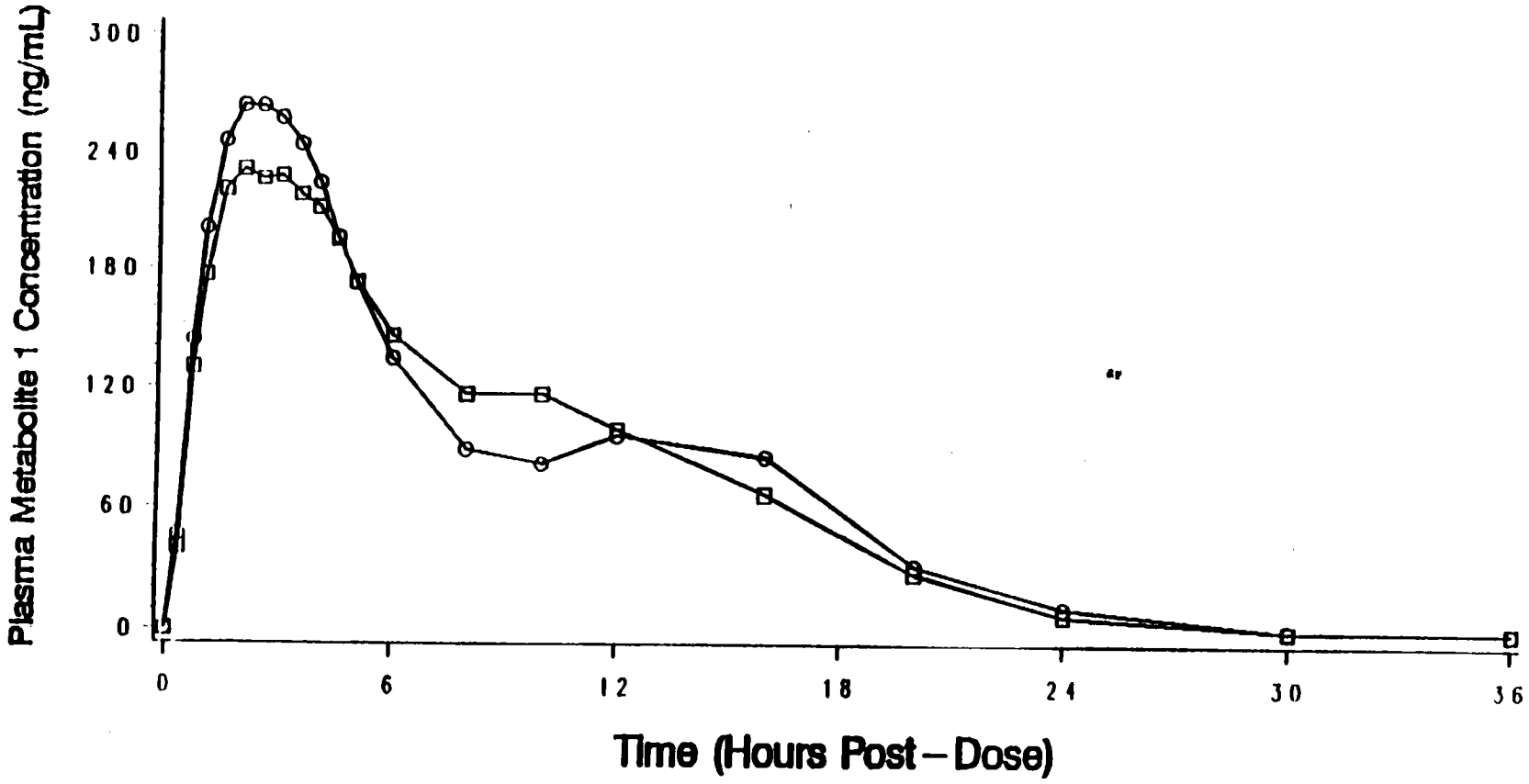

Figure 3

Mean Plasma Metabolite 5 Concentrations (Linear Plot)

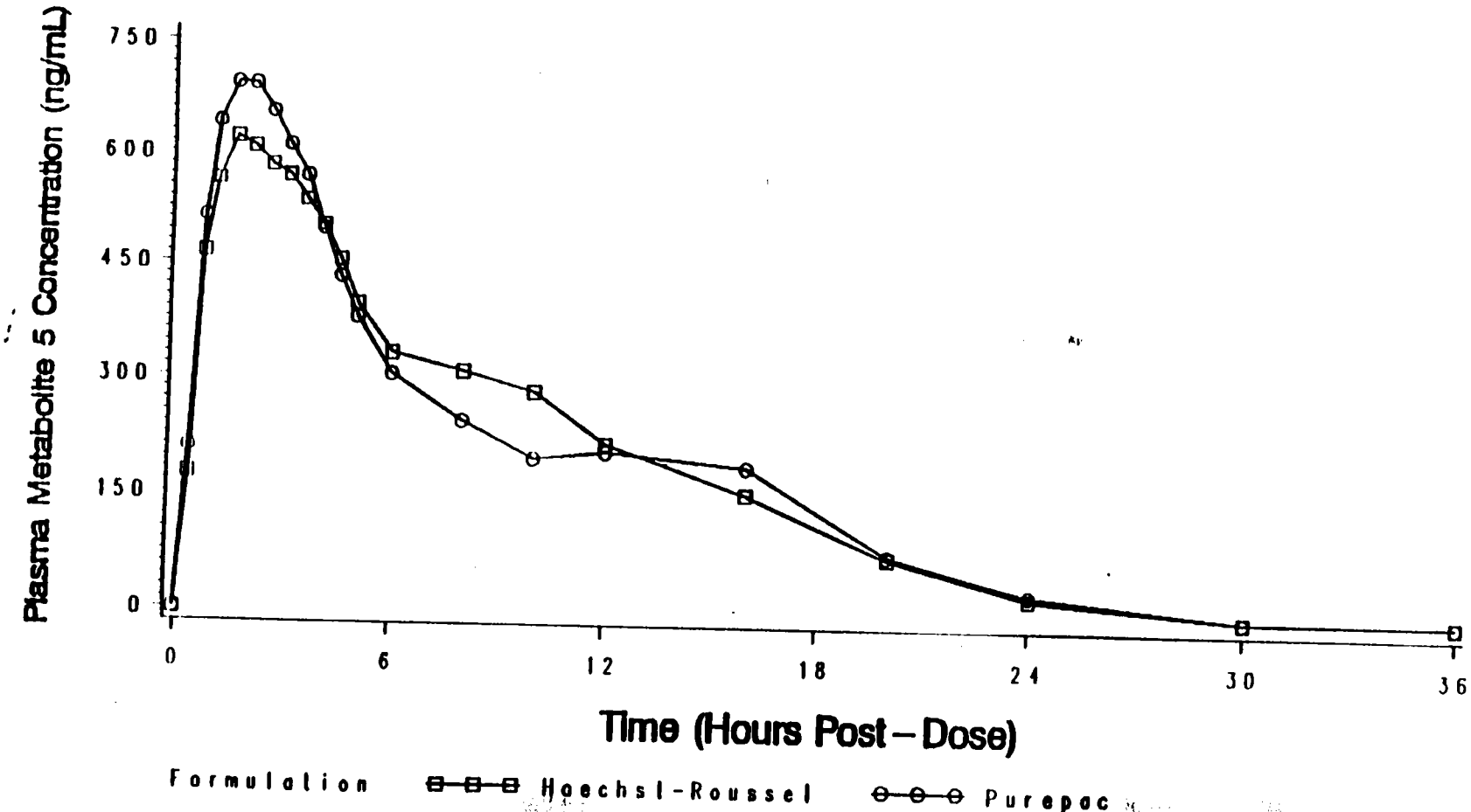

Figure 4

Mean Plasma Pentoxifylline Concentrations (Linear Plot)

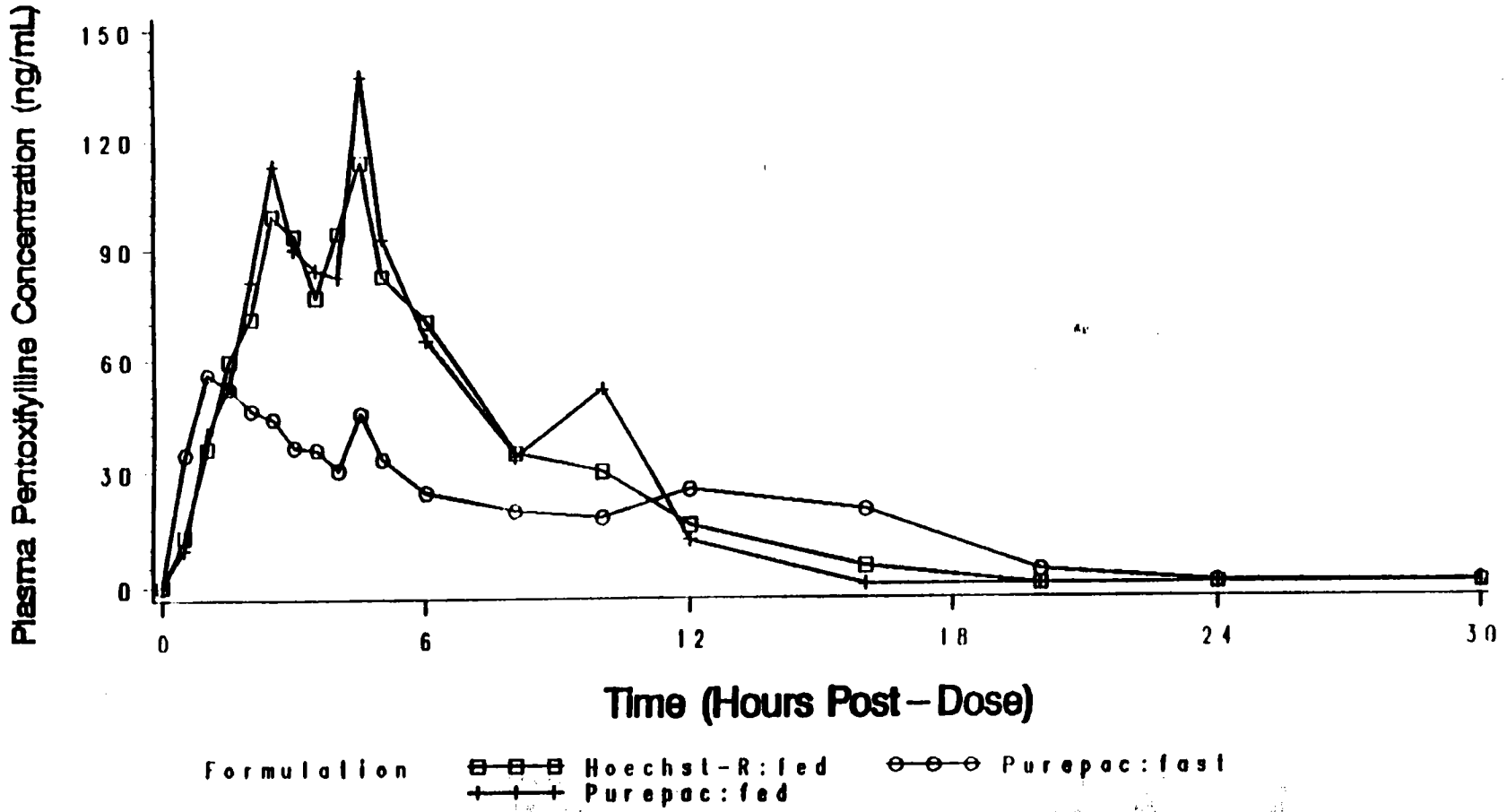

Figure 5

Mean Plasma Metabolite 1 Concentrations (Linear Plot)

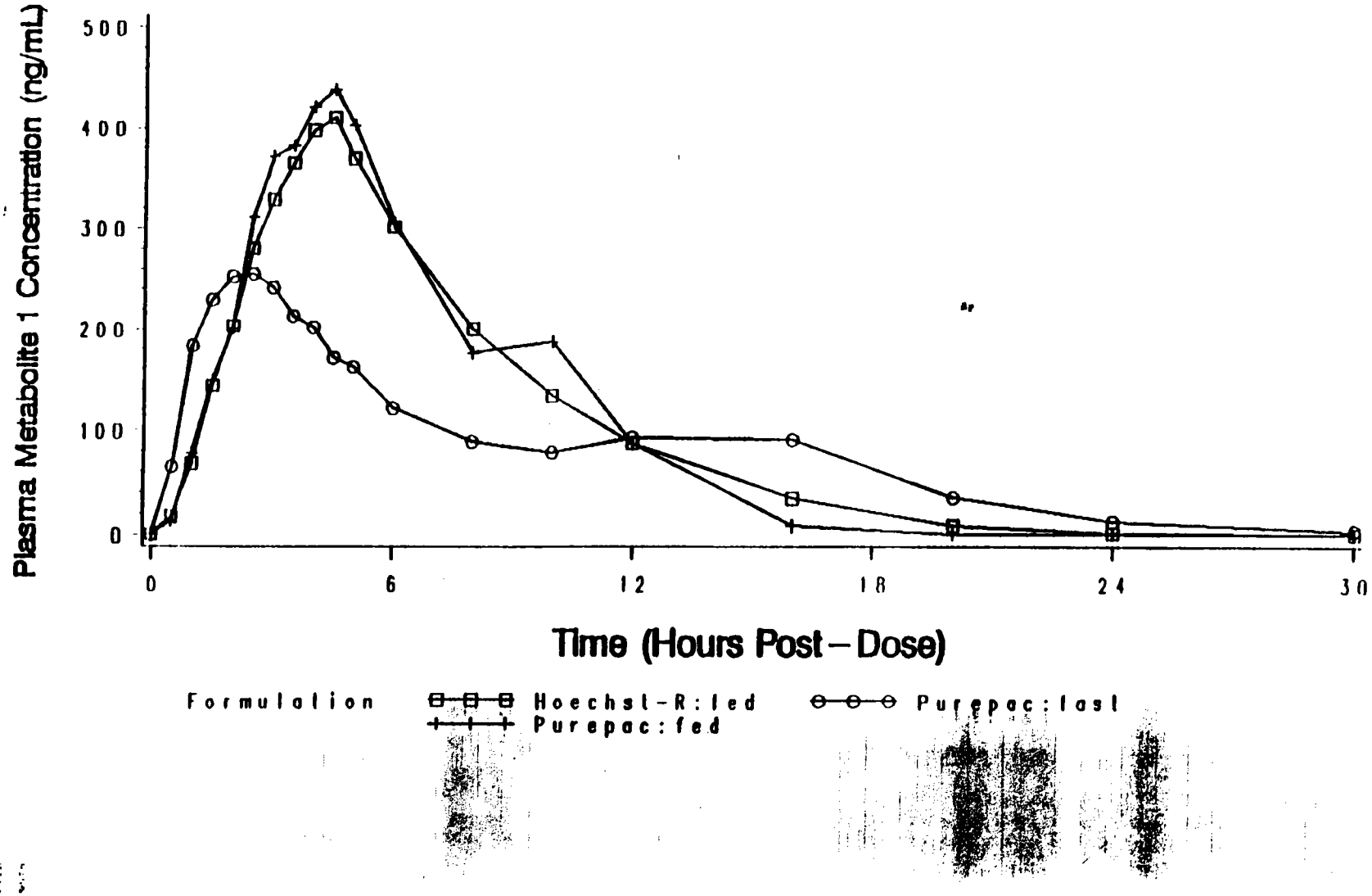

Figure 6

Mean Plasma Metabolite 5 Concentrations (Linear Plot)

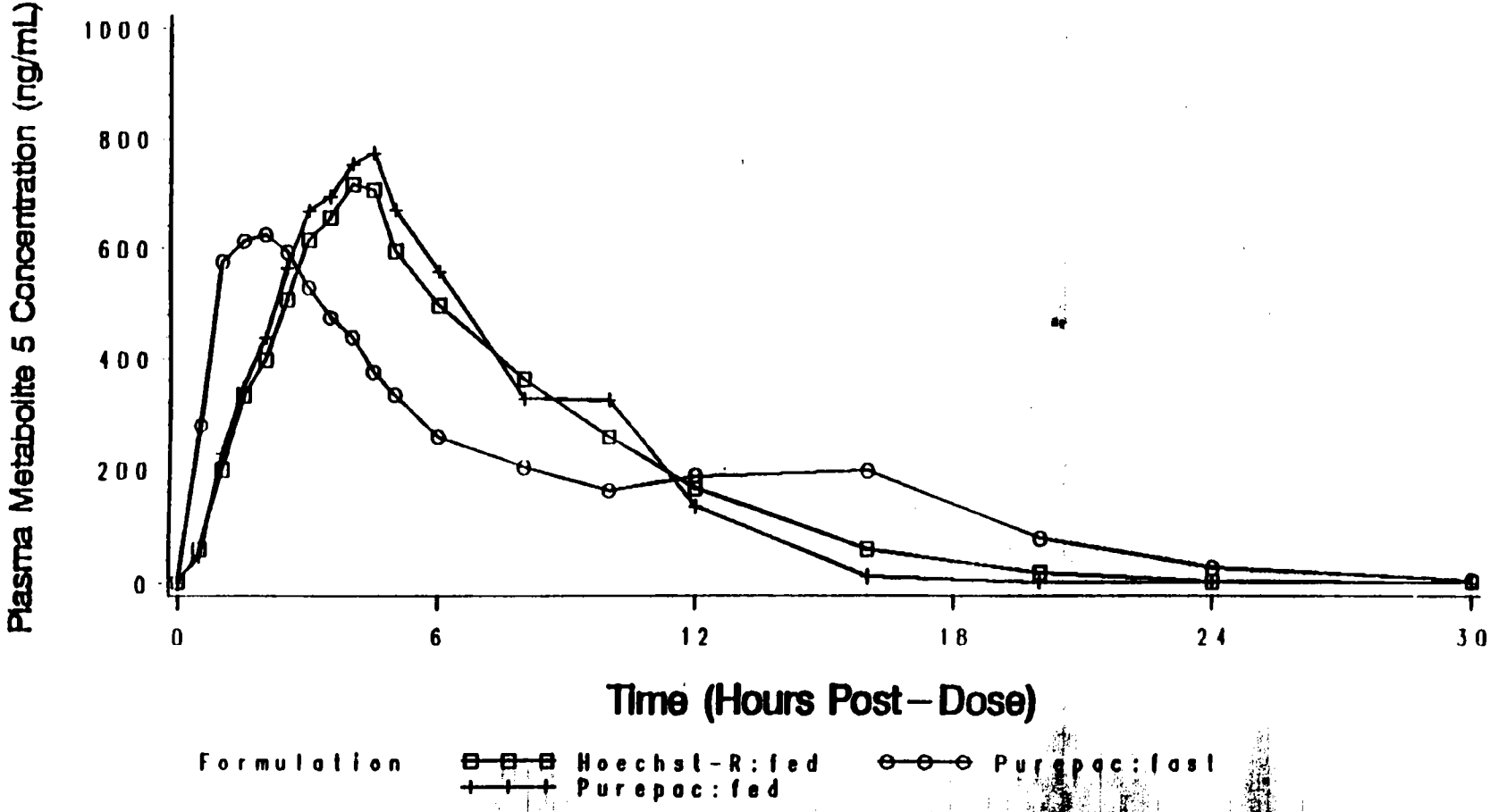

Figure 7

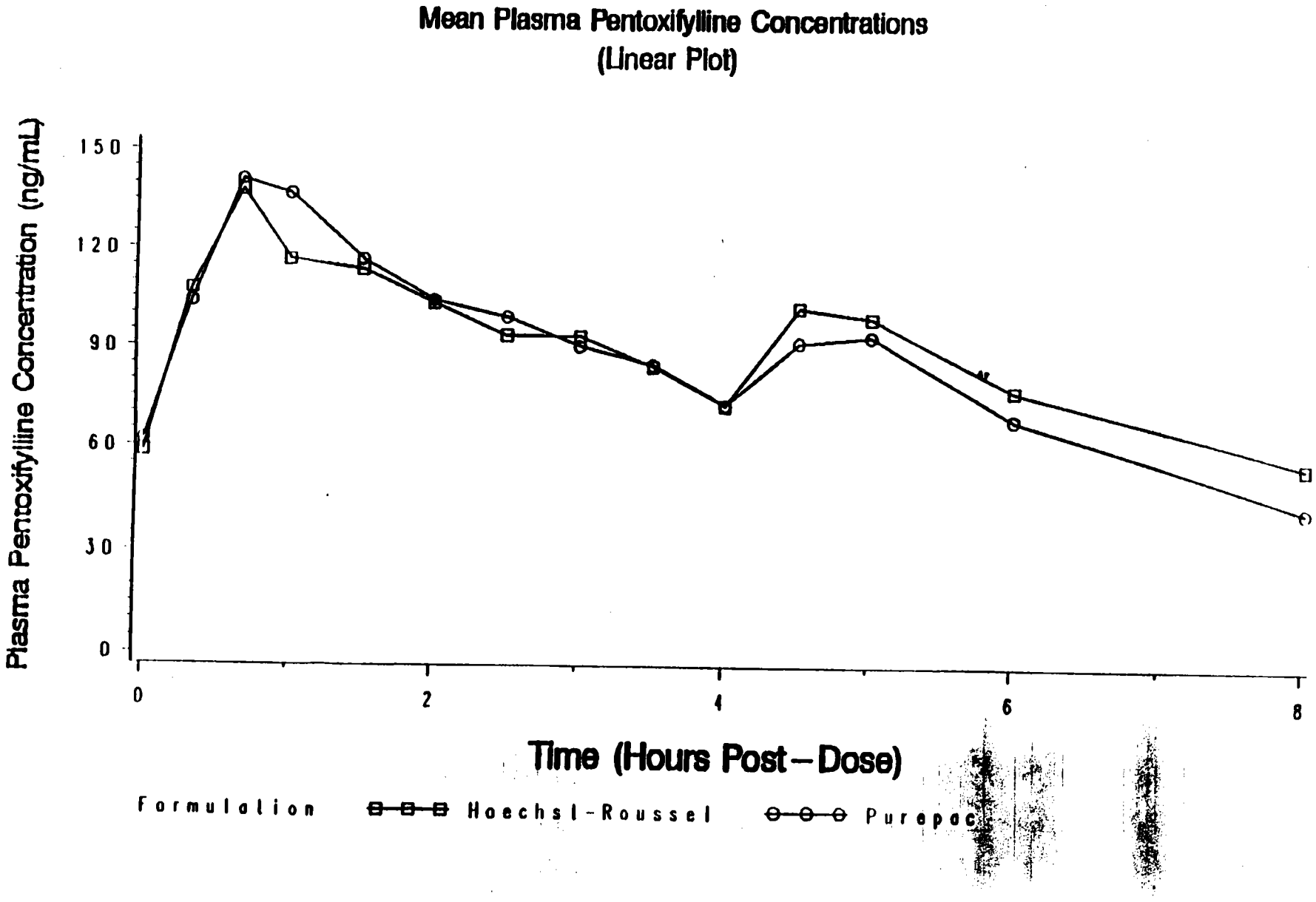
Mean Plasma Pentoxifylline Concentrations
(Linear Plot)
Plasma Pentoxifylline Concentration (ng/mL)
150
120
90
60
30
0
0
2
4
6
8
Time (Hours Post-Dose)
Formulation
Hoechst-Roussel
Purepac

Figure 8

Mean Plasma Metabolite 1 Concentrations
(Linear Plot)

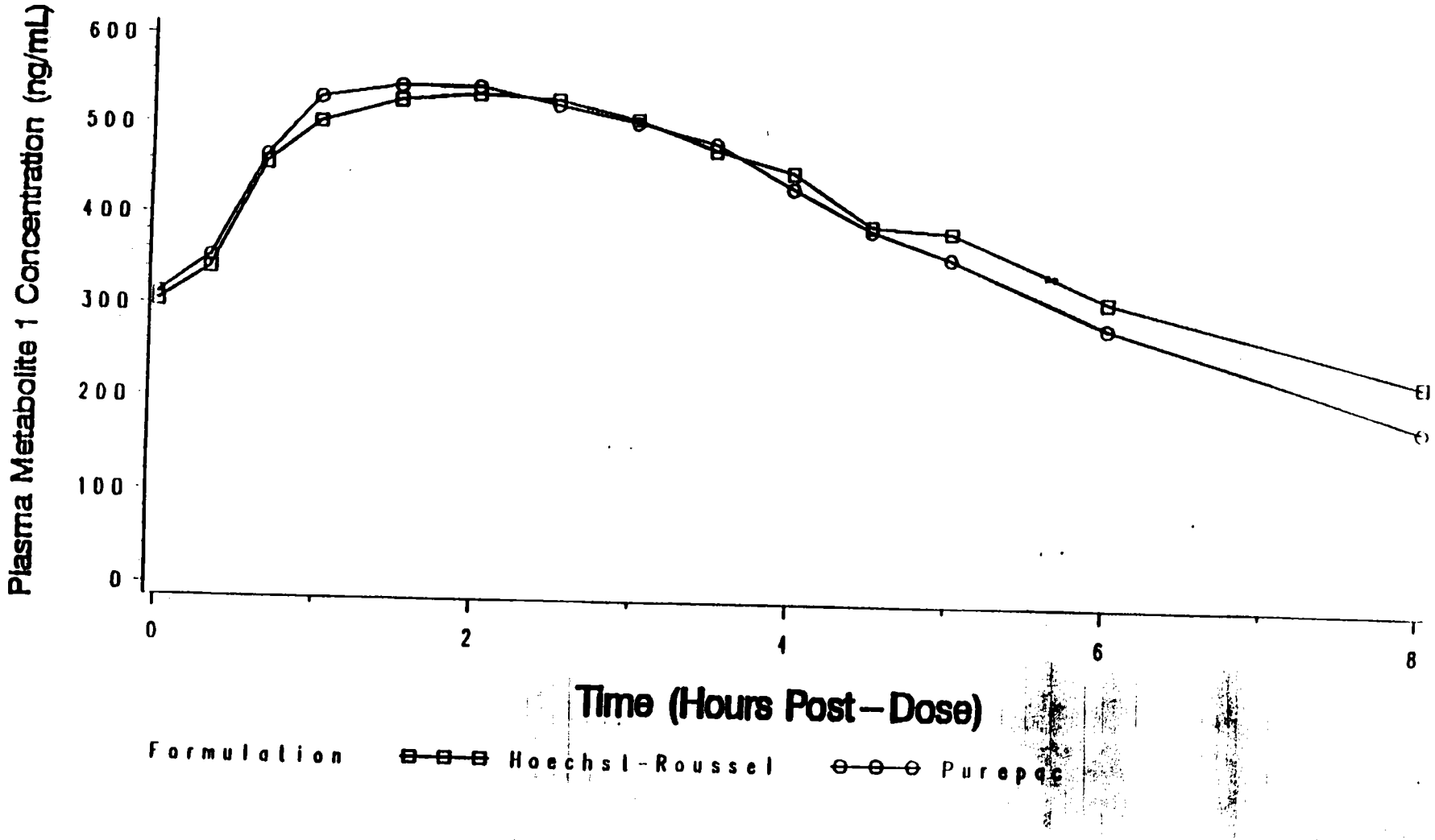

Figure 9

Mean Plasma Metabolite 5 Concentrations
(Linear Plot)